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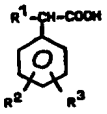
(54) Arylacetic Acid Derivatives

(57) Compounds of the general formula



wherein

R is vinyl or carboxyl,

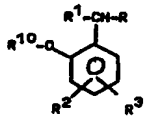
R^1 is hydrogen, methy, or ethyl,

R^2 is hydrogen, fluorine or alkyl having from 1 to 4 carbon atoms, and

R^3 is hydrogen, phenyl, alkoxy having from 1 to 6 carbon atoms, phenoxy or optionally substituted benzoyl or thenpyl, or

R^2 and R^3 together with the phenyl group they are attached to form a naphthyl group, optionally substituted with alkyl and/or alkoxy groups having from 1 to 4 carbons atoms, and

R^{10} is selected from various organic groups, are of interest as intermediates in the preparation of arylacetic derivatives. The compounds wherein R is carboxyl can be catalytically hydrogenated to corresponding derivatives of general formula



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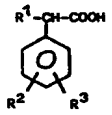
SPECIFICATION

Int rmediates f r th Preparati n of Arylac tic Acid Derivativ s

The present invention relates to some novel chemical intermediates and their conversion to arylacetic acid derivatives of the general formula I



(I),

wherein

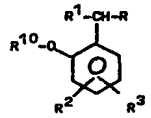
R^1 is hydrogen, methyl or ethyl;

R^2 is hydrogen, fluorine or an alkyl having 1 to 4 carbon atoms;

R^3 is hydrogen, phenyl, alkoxy having 1 to 6 carbon atoms, phenoxy or optionally substituted benzoyl or thenoyl; or

R^2 and R^3 together with the phenyl group they are attached to represent a naphthyl group optionally substituted with one or more alkyl and/or alkoxy groups having 1 to 4 carbon atoms.

Compounds of the general formula I, wherein R^1, R^2 and R^3 have the meanings defined above, are prepared according to the invention starting from compounds of the general formula VIII



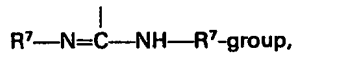
(VIII)

wherein

R is vinyl or carboxyl;

R^{10} is phenyaminocarbonyl, 1-phenyl-5-tetrazolyl, 2-benzoxazolyl, a $—SO_2OMe$ group, wherein Me is a metal atom, preferably sodium or potassium, or an $—SO_2R^6$-group, wherein

R^6 is alkyl having 1 to 4 carbon atoms, 4-methylphenyl, amino, acylamino, alkoxycarbonylamino having 1 to 4 carbon atoms in the alkyl moiety or an



wherein

R^7 is alkyl having 1 to 4 carbon atoms, cycloalkyl having 5 or 6 carbon atoms or tolyl and

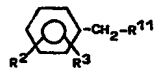
R^1, R^2 and R^3 have the meanings defined above.

Compounds of the general formula VIII are new, and form an important aspect of this invention.

According to the invention compounds of the general formula I, wherein R^1, R^2 and R^3 have the meanings defined above, may be prepared by subjecting new arylacetic acid derivatives of the general formula VIII, wherein R^1, R^2, R^3 and R^{10} have the meanings defined above, and R is carboxyl to catalytic hydrogenation.

It is well known that many of the substituted arylacetic acid derivatives of the general formula I possess valuable antirheumatic and antiinflammatory properties and have small side-effects. These compounds are widely used in human therapy. They are for example described in the US Patent 3,600,437; German Patent 1,941,625; Belgian Patents 621,225 and 787,417; British Patents 971,700 and 1,132,318; French Patents 1,545,270 and 1,549,728 as well as in the Hungarian Patent Application RO-687.

In the majority of the methods known for the preparation of the compounds of the general formula I compounds of the general formula XI



(XI)

wherein

R^{11} is carboxyl, carbalkoxy, optionally substituted carboxylic acid amido or nitrile, and

R^2 and R^3 are as defined above,

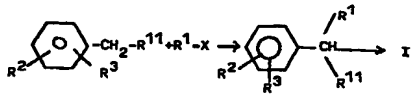
are reacted with alkylating agents of the general formula XII

$$R^1—X \qquad \text{(XII)}$$

wherein

R^1 has the same meaning as defined above and

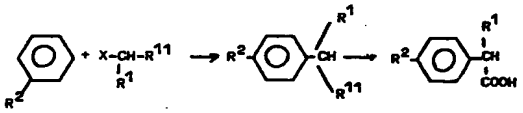
X is halogen or a $CH_3C_6H_4N{=}N—NH$-group, and, if desired, a compound obtained, in which R^{11} is other than carboxyl, is converted into a corresponding compound of the general formula I in a manner known *per se*. The reaction is illustrated on the following Chart A.



and is described in the German Patents 1,668,648 and 1,941,625; US Patents 3,600,437 and 3,755,427, Belgian Patent 752,627 and Holland Patent Application 74,06897.

A common feature of these processes is that their critical step is the formation of a C—C bond between the alkylating agent and the carbon atom adjacent to the carboxyl group. The reaction can either be performed with very moderate yields or affords the final product through more intermediates, which are difficult to purify, and involve complex processing.

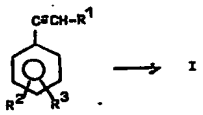
According to other methods an α-substituted alkanecarboxylic acid group is introduced into a suitably substituted aryl ring by electrophilic substitution, and the product obtained is converted into a corresponding free acid. The reaction is illustrated on Chart B below:



wherein R^1, R^2, R^{11} and X have the above-defined meanings. Similar reactions are described in the British Patent 971,700 and in the Belgian Patents 621,225 and 748,534.

Restrictions are placed on these processes, partly due to a potential de-activating effect of certain substituents, e.g. keto group, partly because of their unsatisfactory selectivity.

Another group of known processes involve introducing a branch in the α-position of the alkane carboxylic acid group by isomerisation, as shown on Chart C:



According to the US Patent 3,803,245 thallic nitrate is used for this purpose. This method, however, because of the toxicity of thallium can be industrially used only very carefully, under special precautions.

It has surprisingly been found that compounds of the general formula I, wherein R^1, R^2 and R^3 are as defined above, can be prepared very easily by hydrogenating compounds of the general formula VIII, in which R represents a carboxyl group, and R^1, R^2, R^3 and R^{10} have the above-identified meanings.

In the compounds prepared and used according to the invention the terms "alkyl and alkoxy groups" refer to straight or branched chained hydrocarbon groups, such as methyl, ethyl, isopropyl, *n*-butyl, tertiary butyl and methoxy, ethoxy, isopropoxy groups, respectively.

In the definition of X the term "halogen" preferably represents a chlorine, bromine or iodine atom.

In the definition of R^6 the term "acylamino" preferably indicates an optionally substituted benzoyl or an alkanoyl amino group, having 1 to 5 carbon atoms, e.g. formyl, acetyl, propionyl amino.

In the definition of R^3 and R^6 the optional substituents may be selected from the following groups: amino, nitro, C_{1-4}-alkylamino, C_{1-4}-alkyl-C_{1-4}-alkoxy, halogen.

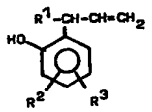
In the definition of Y the term "halogen" preferably refers to a chlorine or bromine atom.

According to a preferred embodiment of the invention arylacetic acid derivatives of the general formula I are prepared by carrying out catalytic hydrogenation in water or in an organic solvent, preferably at a temperature between 20 to 90°C, under a pressure of 1 to 3 atm.

As organic solvents preferably alcohols, more preferably methanol or ethanol; benzene; dioxane; ethylacetate; dimethyl formamide or organic acids, more preferably acetic acid can be used. Reaction is preferably accomplished in the presence of an inorganic base, e.g. alkali metal hydroxide, preferably sodium potassium hydroxide; alkali metal alcoholate, preferably sodium methylate or sodium ethylate; or of an organic base, e.g. triethyl amine.

The compounds of the general formula VIII are new. The present invention concerns also these compounds as well as a process for the preparation of same.

According to the invention compounds of the general formula VIII, wherein R, R^{10}, R^1, R^2 and R^3 are as defined hereinbefore, are prepared by reacting hydroxyl derivatives of the general formula V



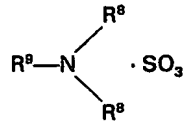
wherein
R^1, R^2 and R^3 are as defined above,
a) with comp unds of the general formula VI

$$R^5—Y \qquad VI$$

wherein
R^5 is 1-phenyl-5-tetrazolyl, 2-benzoxazolyl or an $—SO_2R^6$ group, in which R^6 has the same meaning as defined above, and
Y represents a halogen atom; or
b) with phenylisocyanate; or
c) with compounds of the general formula IX

$$R^7—N=C=N—R^7 \qquad IX$$

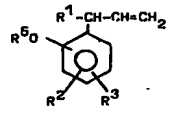
wherein
R^7 has the same meaning as defined above; or
d) with compounds of the general formula X



X

wherein
R^8 is alkyl having from 1 to 4 carbon atoms, and
R^9 is alkyl having from 1 to 4 carbon atoms or phenyl; or
e) with pyridine-sulphur trioxide complex, and, if desired oxidizing a compound of the general formula VIII obtained, in which R is a vinyl group into another compound of the general formula VIII, in which R represents a carboxyl group.

A narrower group of the compounds of the general formula VIII, more particularly compounds of the general formula XIII

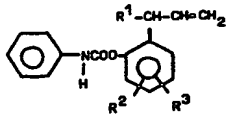


(XIII)

wherein
R^1, R^2 and R^3 and R^5 are as defined hereinbefore, are prepared according to process variant a) of the invention by reacting hydroxyaryl derivatives of the general formula V, wherein R^1, R^2 and R^3 are as defined above, with methane sulphonylchloride, *p*-toluene sulphonylchloride, sulphamoyl chloride, N-benzoyl-sulphamoyl chloride or N-(lower alkoxy) e.g. N-methoxy-sulphamoyl chloride in water and/or in organic solvents. This reaction is preferably carried out at a temperature of 0°C to 40°C.

As an organic solvent pyridine, acetone, methylene chloride or benzene is preferably used and the reaction is preferably accomplished in the presence of an inorganic base, e.g. alkali or alkali earth metal hydroxide or carbonate; or of an organic base, e.g. triethylamine.

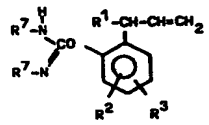
According to a preferred embodiment of process variant b) those compounds of the general formula VIII, which can be encompassed by the general formula XIV



(XIV)

wherein
R^1, R^2 and R^3 are as defined above, can be prepared by reacting a hydroxyaryl derivative of the general formula V, in which R^1, R^2 and R^3 have the meanings defined above, with phenyl isocyanate, optionally in the presence of an organic solvent, preferably petroleum ether. The reaction is preferably carried out at a temperature f 20°C to 100°C, in the presence of an alkaline catalyst, preferably pyridine.

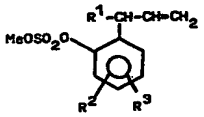
According t process variant c) those compounds of the general f rmula VIII, which can be encompassed by the general formula XV



(XV)

wherein R^1, R^2, R^3 and R^7 are as hereinbefore defined, are prepared by reacting a hydroxyaryl derivative of the general formula V, wherein R^1, R^2 and R^3 have the meanings as defined above, with an excess amount of dicyclohexyl carbodiimide or di-*p*-tolyl-carbodiimide, in the absence of any solvent, preferably at a temperature of 20°C to 100°C.

According to process variant d) those compounds of the general formula VIII, which are encompassed by the general formula XVI



(XVI)

in which R^1, R^2, R^3 and Me are as hereinbefore defined, are prepared by reacting a hydroxyaryl derivative of the general formula V, wherein R^1, R^2 and R^3 are as defined above, with a sulphur trioxide complex of N,N-dimethylaniline, N,N-diethyl-aniline or trimethyl-aniline in an organic solvent, preferably in carbon bisulphide or benzene, at a temperature of −10°C to +40°C, and subsequently treating the reaction mixture with an aqueous solution of an inorganic base. The reaction is preferably carried out in the presence of an excess amount of a base (for example aqueous sodium or potassium hydroxide solution).

According to process variant e) those compounds of the general formula VIII, which are encompassed by the general formula XVI, wherein R^1, R^2, R^3 and Me are as defined above, are prepared by reacting a hydroxyaryl derivative of the general formula V, wherein R^1, R^2 and R^3 have the above-defined meanings, with pyridine-sulphur trioxide complex, in an organic solvent, preferably in carbon bisulphide or benzene, at a temperature between −10°C and +40°C, and treating the reaction mixture obtained with an aqueous solution of an inorganic base. The reaction is performed in the presence of an excess amount of aqueous sodium or potassium hydroxide solution.

The compounds of the general formula VIII, in which R represents a vinyl group can be converted into corresponding compounds of the general formula VIII, in which R is carboxyl by oxidation. The oxidation can for example be carried out with potassium permanganate, in the presence of an organic solvent, preferably at a temperature of 0°C to 40°C. As an oxidizing agent an alkali metal periodate, preferably sodium or potassium periodate can also be successfully used. Suitable solvents are water and/or organic solvents, preferably tert.-amylalcohol, benzene, pentane, methylene chloride, acetone. According to an especially preferred embodiment of the process the process is carried out in the presence of a phase-transforming catalyst and acetic acid. As a catalyst preferably tetrabutyl ammoniumchloride, tetrabutyl-ammoniumbromide, triethyl-benzyl-ammoniumchloride, tricaprilyl-methylammoniumchloride, trioctyl-methyl-ammoniumchloride or benzylhexadecyl-dimethyl-ammoniumchloride or crown ether, preferably 18-crown-6 or dicyclohexyl-18-crown-6 can be used.

Out of the compounds of the general formula V, which are used as starting compounds in the preparation of new compounds of the general formula VIII, the following compounds are thought to be new:

3-isbutyl-6-allyl-phenol,
3-isobutyl-6-(1-methyl-allyl)-phenol,
4-phenoxy-2-(1-methyl-allyl)-phenol,
4-phenoxy-2-allyl-phenol,
2-allyl-6-methoxy-naphthol,
2-(1-methyl-allyl)-naphthol,
4-benzoyl-2-(1-methyl-allyl)-phenol.

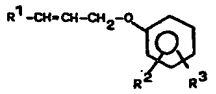
The compounds of the general formula V can be prepared in a manner known *per se*, by reacting compounds of the general formula II

(II)

wherein R^2 and R^3 are as defined above, with compounds of the general formula III

$$R^1—CH=CH—CH_2—X \qquad (III)$$

and subjecting comp unds f th general formula IV



(IV)

obtained to thermal isomerization.

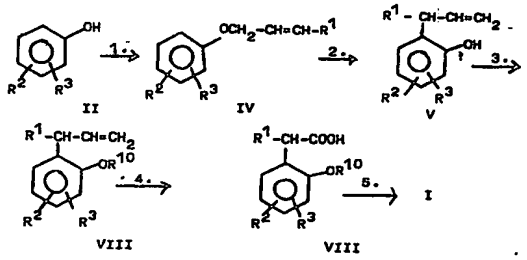
The following compounds of the general formula IV are thought to be new:

2-fluoro-5-allyloxy-diphenyl,
2-fluoro-5-crotyloxy-diphenyl,
(3-isobutylphenyl)-allyl-ether,
(3-isobutyl-phenyl)-crotyl-ether,
4-allyloxy-diphenylether,
4-crotyloxy-diphenylether,
4-crotyloxy-benzophenone,
1-allyloxy-6-methoxynaphthaline,
1-crotyloxy-6-methoxy-napthhaline.

The aryloxy derivatives of the general formula IV are preferably prepared in water and/or in an organic solvent, preferably acetone, dimethyl formamide, ether, in the presence of a base, preferably potassium carbonate or sodium carbonate, at a temperature of 20°C to 100°C.

The thermal isomerization of the compounds of the general formula IV is preferably effected at 150°C to 260°C in the absence of any solvent or in an organic solvent, preferably, N,N-dimethylaniline, N,N-diethylaniline, dimethyl formamide or diphenyl ether.

According to the process provided by this invention compounds of the general formula I can be prepared starting from compounds of the general formula II in an entirely new manner, through new intermediates as illustrated on Chart D.



The process according to the invention is considerably easier to carry out also on industrial scale than the processes known in the art.

Further details of the invention are illustrated by the following illustrative and non-limiting Examples.

Example 1

To a solution of 19.8 g. of 4-hydroxy-benzophenone in 100 ml. of dry acetone 18.3 g. of crotyl bromide and 14 g. of anhydrous potassium carbonate are added. The reaction mixture is boiled for 4 hours with stirring and acetone is distilled off. The residue is treated with water and the separated oil is taken up in ether. The ethereal solution is washed with a dilute aqueous sodium hydroxide solution and subsequently with water, and is then dried over sodium sulphate. Upon distilling off ether 4-crotyloxy-benzophenone is obtained as a pale yellow oil, which crystallizes in one to two days to afford a product melting at 36°C.

Example 2

A solution of 5 g. of 4-crotyloxy-benzophenone in 15 ml, of diphenyl ether is boiled for one hour. It is allowed to cool and is diluted with petroleum ether. The solution obtained is extracted with a 5 N sodium hydroxide solution. The alkaline phase is acidified with a dilute aqueous hydrochloric acid solution, the precipitated crystals are filtered off with suction and recrystallized from cyclohexane to give 4-benzoyl-2-(1-methyl)-allylphenol, melting at 111°C to 113°C.

Example 3

To a solution of 104 ml. of *o*-cresol in 200 ml. of acetone a solution of 40.8 g. of sodium hydroxide in 160 ml. of water is added. To the reaction mixture 104 ml. of crotyl bromide are added dropwise, with stirring, under cooling with ice-water. Stirring is continued for further 2 hours, whereupon the mixture is brought to the boil and boiled for an additional hour. After cooling the organic phase is separated, the aqueous phase is shaken with two 50-ml. portions of petroleum ether. The combined organic phases are shaken with eight 100-ml. portions of a 30% aqueous sodium

hydroxide solution and washed to neutral with water. Upon distilling off petr luem ether *o*-cresol-cr tyl ether is obtained as a yellow, oily residue.

o-cresol-crotyl ether obtained is refluxed until the boiling point arises to 210°C (about 4 hours). After cooling 160 ml. of a 20% aqueous potassium hydroxide solution are added and the reaction mixture is shaken with three 50-ml. portions of petroluem ether. The aqueous solution is acidifed with a concentrated hydrochloric acid solution. The separated oil is taken up in ether, the ethereal solution is washed to neutral with water and dried over sodium sulphate. Ether is distilled off and the remaining oil is subjected to distillation *in vacuo* to afford 2-methyl-6-(1-methyl)-allylphenol. n_D^{25}=1.5315.

Example 4

8.62 g. of 4-phenoxy-phenyl-crotyl ether (prepared according to DOS 2,304,962) in 30 ml. of diphenyl ether are refluxed for one hour at 260°C. The reaction mixture is cooled to room temperature, diluted with 30 ml. of petroleum ether and shaken with two 25-ml. portions of Claisen-alkali. The alkaline phase is acidified with a concentrated aqueous hydrochloric acid solution and shaken with three 30-ml. portions of ether. The combined ethereal phases are dried over sodium sulphate and evaporated to give 2-(1-methyl-allyl)-4-phenoxy-phenol.

Example 5

To a solution of 48.7 g. of 2-allylphenol in 176 ml. of dry pyridine 34 ml. (51.3 g.) of mesyl chloride are added dropwise, with stirring, under cooling. The reaction mixture is allowed to stand for 2 hours and is then poured on a mixture of concentrated hydrochloric acid and ice. The precipitated oil is taken up in ether, the ethereal solution is washed with a 2 N sodium hydroxide solution and subsequently with water, and is dried over sodium sulphate. Ether is distilled off to give 69.4 g. of 2-allyl-phenol mesylester. n_D^{25}=1.5191.

Example 6

To a cooled solution of 14.7 g. of 2-(1-methyl)-allyl-phenol in 50 ml. of dry pyridine 14.5 g. of mesyl chloride are added dropwise, with stirring. The reaction mixture is allowed to stand overnight, whereupon it is poured onto a mixture of concentrated hydrochloric acid and ice. The separated oil is taken up in ether. The ethereal solution is washed with a 2 N sodium hydroxide solution and subsequently with water, and is then dried over sodium sulphate. Ether is distilled off to give 20 g. of 2-(1-methyl)-allyl-phenol mesylester. n_D^{25}=1.5197.

Example 7

Following the procedure described in Example 6 but replacing 2-(1-methyl)-allyl-phenol by 18.4 g of 2-allyl-1-naphthol 20.5 g. of 2-allyl-1-naphthol mesylester are obtained as a slowly solidifying oil. The oiling product crystallizes in 1 to 2 days and the melting point of the crystals obtained amounts to 45°C.

Example 8

To a cooled solution of 33.8 g. of 2-allyl-phenol in 125 ml. of dry pyridine 47.5 g. of *p*-toluene-sulphonic acid chloride are added in small portions, with stirring. The mixture is stirred for three hours whereupon it is poured onto the mixture of concentrated hydrochloric acid and ice. Futheron the procedure described in Example 6 is followed. 2-allyl-phenol tosylester is obtained. n_D^{25}=1.5543.

Example 9

A mixture of 13.5 g. of 2-allyl-phenol, 13.1 g. of phenylisocyanate and 0.5 g. of pyridine is kept at 100°C for five minutes. Petroleum ether is added whereupon the precipitated crystals are filtered off with suction and washed with petroleum ether to give 2-allyl-phenol-phenyl-urethane, melting at 108°C to 109°C.

Example 10

Following the procedure described in Example 9 but starting from 18.4 g. of 2-allyl-1-naphthol, 13.1 g. of phenylisocyanate and 0.5 ml. of pyridine and recrystallizing the product obtained from carbon tetrachloride 2-allyl-1-naphthol-phenyl-urethane is prepared, melting at 141°C to 142°C.

Example 11

Following the procedure described in Example 9 but starting from 3.4 g. of 2-(1-methyl)-allyl-phenol, 3.3 g. of phenyl-isocyanate and 0.1 ml. of pyridine 2-(1-methyl)-allyl-phenol-phenyl-urethane is obtained, melting at 92°C to 94°C.

Example 12

Following the procedure described in Example 9 but starting fr m 8.4 g. of 2-(1-m thyl)-allyl-1-naphthol, 8.7 g. of phenylisocyanate and 0.2 ml. of pyridin 2-(1-methyl)-allyl-1-naphth l-phenyl-urethane is obtained, melting at 138°C to 142°C.

Exampl 13

To a solution of 22 g. of 2-methyl-6-allyl-ph nol [J. Org. Chem. *30*, 1032 (1965)] in 90 ml. f dry pyridine 24.6 g. of methanesulphonic acid chloride are added dropwise, with stirring, under co ling with ice-water. The reaction mixture is allowed to stand at room temperature overnight, and the reaction mixture containing crystals is poured onto a mixture of 50 ml. of concentrated hydrochloric acid and 150 g. of ice. The oily phase is separated and the aqueous phase is extracted with two 100-ml. portions of ether. The ethereal solution is combined with the oil, it is shaken with two 100-ml. portions of a 1:1 mixture of hydrochloric acid and water, then washed to neutral with water and dried over sodium sulphate. Ether is distilled off and 2-methyl-6-allyl-phenol mesylester is obtained as a yellow oil. $n_D^{25}=1.5252$.

Example 14

To a solution of 4.28 g. of 3-(1-methyl)-allyl-4-hydroxy-benzophenone in 20 ml. of dry pryidine 2.2 g. of methane-sulphonic acid chloride are added, and the reaction mixture is heated on water-bath for five hours. The reaction mixture is cooled and is poured on the mixture of 10 ml. of concentrated hydrochloric acid and 100 g. of ice. The oily phase is shaken with three 50-ml. portions of ether. The combined ethereal extracts are shaken with three 20-ml. portions of 2 N hydrochloric acid, washed to neutral with water, shaken with two 20-ml. portions of a 2 N sodium hydroxide solution, washed with water again and finally dried over sodium sulphate. Evaporation of the product affords 3-(1-methyl)-allyl-4-mesyloxy-benzophenone as a yellow oil. $n_D^{22}=1.5732$.

Example 15

To a solution of 14.8 g. of 2-allyl-4-methyl-phenol [J. Am. Chem. Soc. *80*, 3271 (1958)] in 50 ml. of dry pyridine 14 g. of methane-sulphonic acid chloride are added dropwise, with stirring, under cooling with ice-water. Furtheron the procedure described in Example 13 is followed. Distilling off the ether 2-allyl-4-methylphenol mesyl ester is obtained as a yellow oil.

Example 16

To a solution of 16.2 g. of 2-(1-methyl)-allyl-4-methyl-phenyl [Helv. *45*, 1943 (1962)] in 60 ml. of dry pyridine 18.43 g. of methanesulphonic acid chloride are added dropwise, with stirring, under cooling with ice-water. Furtheron following the procedure described in Example 13 and distilling off the ether 2-(1-methyl)-allyl-4-methylphenol mesylester is obtained as a yellow oil. $n_D^{28}=1.5053$.

Example 17

To a solution of 32.44 g. of 2-methyl-6-(1-methyl)-allyl-phenol in 120 ml. of dry pyridine 33.2 g. of methane-sulphonic acid chloride are added dropwise, with stirring, under cooling with ice-water. Furtheron following the procedure described in Example 13 and distilling off ether 2-methyl-6-(1-methyl)-allyl-phenol mesylester is obtained, which is distilled *in vacuo*. Boiling point: 187°C to 190°C/15 mmHg.; $n_D^{21}=1.5283$.

Example 18

7.17 g. of 2-(1-methyl-allyl)-4-phenoxy-phenol are dissolved in 30 ml. of pyridine and 3.41 g. of mesyl chloride are added dropwise, with cooling. The reaction mixture is allowed to stand in a refrigerator overnight, and is then poured onto a mixture of ice and 12 ml. of concentrated hydrochloric acid. The oily phase is shaken with three 20-ml portions of benzene. From the combined benzene fractions unmesylated phenyl derivative is eliminated with two 20-ml. portions of Claisen-alkali, and the organic phase is washed to alkaline-free. The benzene solution is dried over sodium sulphate and is evaporated. Thus 2-(1-methyl-allyl)-4-phenoxy-phenyl-mesyl ester is obtained. $n_D^{22}=1.5565$.

Example 19

2 g. of 2-allyl-4-phenoxy-phenol are dissolved in 10 ml. of pyridine and to the cooled solution of 1 g. of mesyl chloride is added dropwise. The reaction mixture is allowed to stand overnight and is then poured onto a mixture of ice and 5 ml. of concentrated hydrochloric acid. The separated oil is eliminated by extraction with three 20-ml. portions of ether. The combined ethereal solutions are shaken with two 10-ml. portions of 1 N sodium hydroxide, whereupon it is washed to neutral with water. The ethereal solution is dried over sodium sulphate. Evaporation of the product affords 2-allyl-4-phenoxy-phenyl mesylester.

Example 20

To a solution of 7.7 g. of 3-allyl-4-hydroxy-benzophenone [J. Am. Chem. Soc. *80*, 3271 (1958)] in 43 ml. of dry pyridine 4.46 g. of methanesulphonic acid chloride are added dropwise, with stirring, under cooling with ice-water. Furtheron the procedure described in Example 13 is followed. After distilling off ether 3-allyl-4-mesyloxy-benzophenone is obtained as a yellowish brown il.

Exampl 21

To a solution f 19.8 g. of potassium permanganate in 1500 ml. of acetone a soluti n f 5.3 g. of

2-allyl-phenol mesylester in 10 ml. of acetone is added dropwise, with stirring, under co ling. Th reaction mixtur is allowed to stand overnight, and thereafter is acidified with a 5 N sulphuric acid solution and filtered. The filtrate is evaporated *in vacuo*. The crystalline residue is admixed with a sodium hydrogencarbonate solution, filtered and the filtrate is acidified with a 5 N hydrochloric acid solution. The precipitated crystals are filtered off with suction to give 2-mesyloxy-phenyl-acetic acid, melting at 110°C. After recrystallization from a 50% ethanol solution the melting point amounts to 125°C to 126°C.

Example 22

To a suspension of 31.6 g. of potassium permanganate in 300 ml. of water a solution of 12.7 g. of 2-allyl-phenol mesylester, 60 ml. of acetic acid and 1.35 g. of tetrabutyl ammoniumchloride in 300 ml. of methylene chloride is added with stirring, under cooling with ice-water. The reaction mixture is stirred for 30 minutes with stirring, then 34 g. of sodium hydrogensulphite and 60 ml. of a 1:1 mixture of hydrochloric acid and water are added. The methylene chloride phase is separated and the aqueous phase is shaken with two 100-ml. portions of methylene chloride. The methylene chloride solution is dried over sodium sulphate. The crystalline substance obtained after distilling off methylene chloride is dissolved in 70 ml. of sodium hydrogencarbonate and the solution obtained is shaken with methylene chloride. The aqueous solution is acidified with a 2 N aqueous hydrochloric acid solution. The precipitated crystals are filtered with suction and dried. Thus 2-mesyloxy-phenylacetic acid is obtained, melting at 123°C to 124°C.

Example 23

To a suspension of 15.8 g. of potassium permanganate in 150 ml. of water a solution of 6 g. of 2-(1-methyl)-allylphenol-mesylester, 30 ml. of acetic acid and 0.7 g. of tetrabutyl ammoniumchloride in 150 ml. of benzene is added with stirring, under cooling. Furtheron following the procedure described in Example 22 and filtering off the product obtained with suction 2-mesyloxy-hydrotropic acid is prepared, melting at 94°C to 96°C.

Example 24

Following the procedure described in Example 22 but starting from 7.9 g. of 2-allyl-naphthol mesylester crystalline 1-mesyloxy-2-naphthyl-acetic acid is obtained, melting at 180°C to 181°C.

Example 25

Following the procedure described in Example 22 but replacing 2-allyl-phenol mesylester by 8.54 g. of 2-tosyloxy-phenylacetic acid 2-tosyloxy-phenylacetic acid is obtained, melting at 119°C to 120°C.

Example 26

To a suspension of 15.8 g. of potassium carbonate in 150 ml. of water 6.8 g. of 2-allyl-4-methyl mesylester are added under ice-cooling, with stirring. Furtheron following the procedure described in Example 22 2-mesyloxy-5-methylphenylacetic acid is obtained as a white crystalline substance. Recrystallization from a 50% aqueous ethanol solution affords a product melting at 101°C to 102°C.

Example 27

Following the procedure described in Example 22 but starting from 7.2 g. of 2-(1-methyl)-allyl-4-methylphenol mesylester 2-mesyloxy-5-methyl-hydrotropic acid is obtained in the form of white crystals, melting at 122°C to 123°C.

Example 28

To a suspension of 8.4 g. of potassium permanganate in 84 ml. of water a solution of 3.3 g. of 3-(1-methyl)-allyl-4-mesyloxy-benzophenone, 0.34 g. of tetrabutyl ammonium chloride and 31 ml. of acetic acid in 84 ml. of benzene is added with stirring. Furtheron following the procedure described in Example 22 a viscous substance is obtained, which is shaken with three 20-ml. portions of ether. Upon addition of cyclohexyl amine the cyclohexyl amine salt of 2-mesyloxy-5-benzoyl-hydratropic acid is obtained as a white crystalline substance, melting at 151°C.

Example 29

To a suspension of 57.12 g. of potassium permanganate in 542 ml. of water a solution of 24.58 g. of 2-methyl-6-(1-methyl)-allyl-phenol mesylester, 2.42 g. of tetrabutyl ammoniumchloride and 216 ml. of acetic acid in 542 ml. of benzene is added with stirring, under cooling with ice-water. Furtheron following the procedure described in Example 22 2-mesyloxy-3-methyl-hydratropic acid precipitates as a white crystalline substance. The crystals are filtered ff with suction. Melting point: 138°C t 142°C.

Example 30

T a suspension of 25.6 g. of potassium permanganate in 250 ml. f water a s luti n of 9.2 g. f

3-allyl-4-mesyloxy-benzophenone, 1 g. of tetrabutyl ammoniumchloride and 90 ml. of acetic acid in 250 ml. of benzene is added at room temperature with stirring. Furtheron following the proc dure described in Example 22 2-mesyloxy-5-benzoylphenylacetic acid is obtained as a white crystalline product. After filtering off with suction and recrystallization from abs. ethanol the product melts at 154°C to 155°C.

Example 31

To a suspension of 33.2 g. of potassium permanganate in 315 ml. of water a solution of 14.2 g. of 2-methyl-6-allyl-phenol mesylester, 126 ml. of acetic acid and 1.4 g. of tetrabutyl ammoniumchloride in 315 ml. of benzene is added with stirring, under cooling with ice-water. Furtheron following the procedure described in Example 22 2-mesyloxy-3-methyl-phenylacetic acid is obtained as a white crystalline product, melting at 121°C to 124°C.

Example 32

6.85 g. of 2-(1-methyl-allyl)-4-phenoxy phenylmesylester are dissolved in 180 ml. of benzene containing 0.73 g. of tetrabutyl ammoniumchloride and 67 ml. of glacial acetic acid. The solution obtained is added to a solution of 19 g. of potassium permanganate in 180 ml. of water with stirring. Furtheron following the procedure described in Example 22 a slowly solidifying oily product is obtained. Melting point of the crystalline product obtained after standing amounts to 113°C to 118°C. After recrystallization from 30 ml. of diisopropyl ether the melting point of 2-mesyloxy-5-phenoxyhydratropic acid is 123°C to 125°C.

Example 33

1.53 g. of 2-allyl-4-phenoxy phenylmesylester are dissolved in 47 ml. of benzene containing 0.2 g. of tetrabutyl ammoniumchloride and 17 ml. of glacial acetic acid. The solution obtained in poured into a solution of 5 g. of potassium permanganate in 47 ml. of water. Furtheron following the procedure described in Example 22 an oily product is obtained, which is dissolved in a 1 N solution of sodium hydrogencarbonate. The solution obtained is shaken with two 10-ml. portions of benzene, whereupon the alkaline phase is acidifed with a concentrated hydrochloric acid solution and shaken with three 10-ml. portions of ether. The combined ethereal extracts are dried and evaporated to give 2-mesyloxy-5-phenoxy phenylacetic acid, melting at 121°C.

Example 34

To a solution of 33 g. of 2-methane-sulphonyloxy-3-phenoxy-hydratropic acid in 200 ml. of methanol 28 ml. of triethyl amine and 2 g. of a 5% palladium on charcoal catalyst are added at 25°C. The mixture is then hydrogenated under atmospheric pressure until a calculated amount of hydrogen is used up. The catalyst is filtered off and the solution is evaporated. The evaporation residue is taken up in water, acidified with a 20% aqueous hydrochloric acid solution and the separated oil is extracted with chloroform. The chloroform solution is evaporated after drying over sodium sulphate, and the residue is distilled off. 23 g. (95%) of 3-phenoxy-hydratropic acid are obtained, boiling at 190°C to 192°C (0.4 mmHg.). $n_D^{25}=1.5751$. Melting point of the corresponding cyclohexylamine salt amounts to 153°C to 154°C.

Example 35

Following the procedure described in Example 34 but starting from

32.5 g. of 2-(1-methane-sulphonyloxy-6-methoxy-2-napthyl)-propionic acid,
34 g. of 2-methanesulphonyloxy-4-phenyl-5-fluoro-hydratropic acid,
35 g. of 2-methanesulphonyloxy-5-benzoyl-hydratropic acid and
24.5 g. of 1-methane-sulphonyloxy-2-naphthyl-acetic acid, respectively the following end product are obtained:

End product	*melting point (°C)*
22 g. of 2-(6-methoxy-2-naphthyl)-propionic acid	153 to 155
23.3 g. of 3-fluoro-4-phenyl-hydratropic acid	110 to 111
24.4 g. of 3-benzoyl-hydratropic acid	90 to 92 and
16 g. of 2-naphthyl-acetic acid	141 to 142, resp.

Example 36

To a solution of 77.5 g. of 2-methane-sulphonyloxy-4-methyl-hydratropic acid in 600 ml. of methanol 84 ml. of triethyl amine and 6 g. of a 5% palladium on charcoal catalyst are obtained, and the mixture is hydrogenated at 25°C until a calculated amount of hydrogen is used up. Catalyst is filtered off and the filtrate is evaporated. The residue is taken up in water and the solution is acidified with a 20% aqueous hydrochloric acid solution. The separated 4-methyl-hydratropic acid is extracted with chloroform and the chloroform extract is dried over sodium sulphate. Evaporation f the soluti n affords 4-methyl-hydratr pic acid.

Example 37

To a solution of 24.5 g. of 2-methane-sulphonyloxy-hydratropic acid in 200 ml. f methan l 28 ml. of triethyl amine and 2 g. of a 5% palladium-on-charc al catalyst are added. The mixture is hydrogenated at 25°C, under atmospheric pressure until a calculated amount of hydrogen is used up. The catalyst is filtered off and the filtrate is evaporated. The residue is taken up in water and acidified with a 20% aqueous hydrochloric acid solution. The separated hydratropic acid is extracted with chloroform. The chloroform solution is dried over sodium sulphate, evaporated and the residue is distilled off. 13.5 g. (90%) of hydratropic acid are obtained, boiling at 145°C (13 mmHg.); n_D^{25}=1.5219.

Example 38

To a solution of 4.1 g. of 2-toluene-sulphonyloxy-3-phenoxy-hydratropic acid in 150 ml. of alcohol 24 g. of a W-6 nickel catalyst are added, and the mixture is hydrogenated at 25°C, under atmospheric pressure until a calculated amount of hydrogen is used up. The catalyst is filtered off, the filtrate is evaporated and the residue is taken up in water and acidified with a 10% aqueous hydrochloric acid solution. The separated oil is extracted with chloroform, the chloroform solution is dried over sodium sulphate and evaporated, 2.1 g. (89%) of 3-phenoxy-hydratropic acid are obtained. Melting point of the corresponding cyclohexylamine salt amounts to 151°C to 153°C.

Example 39

To a solution of 3.3 g. of 2-toluene-sulphonyloxy-4-methyl-hydratropic acid in 150 ml. of alcohol 15 g. of Raney nickel are added as a catalyst and the reaction mixture is boiled for three hours with stirring. Upon cooling the catalyst is filtered off and the filtrate is evaporated. The residue is triturated with 50 ml. of water and the separated product is extracted with chloroform. Evaporation of the chloroform extract affords 1.5 g. (91%) of 4-methyl-hydratropic acid.

Example 40

To a solution of 3.4 g. of 2-amino-sulphonyloxy-3-phenoxy-hydratropic acid in 20 ml. of methanol 2.8 ml. of triethylamine and 0.2 g. of a 5% palladium-on-charcoal catalyst are added. The mixture is hydrogenated at 25°C, under atmospheric pressure until a calculated amount of hydrogen is used up. The catalyst is filtered off and the filtrate is evaporated. The evporation residue is taken up in water, acidified with a 20% aqueous hydrochloric acid solution and the separated oil is extracted with chloroform. The chloroform extract is dried over sodium sulphate and is evaporated to give 2.2 g. (91%) of 3-phenoxy-hydratropic acid. Melting point of the corresponding cyclohexylamine salt amounts to 151°C to 153°C.

Example 41

Following the procedure described in Example 40 but starting from

4.5 g. of 2-(N-benzoylamino-sulphonyloxy)-5-benzoylhydrotropic acid;
3.8 g. of 2-[1-(N-methoxy-carbonylamido-sulphonyloxy)-6-methoxy-2-naphthyl]-propionic acid and
2.44 g. of 2-mesyloxy-3-methyl-phenylacetic acid, respectively the following end products are obtained:

End product	*Melting point (°C)*
2.35 g. of 2-benzoyl-hydratropic acid	90 to 92
2.2 g. of 2-(6-methoxy-2-naphthyl)-propionic acid	153 to 155
3-methyl-phenylacetic acid	67 to 69, resp.

Example 42

To a solution of 4.2 g. of 2-hydroxy-3-phenoxy-hydratropic acid sulphate dipotassium salt in 50 ml. of water 2 g. of potassium hydroxide and 2 g. of a Raney nickel catalyst prepared freshly according to Ureshibara, and the reaction mixture is stirred at 60°C for 10 to 15 minutes. The catalyst is filtered off and the filtrate is acidified with a 20% aqueous hydrochloric acid solution. The separated solution is extracted with chloroform and the chloroform solution is dried over sodium sulphate and evaporated. 2.35 g. (97%) of 3-phenoxy-hydratropic acid are obtained. Melting point of the corresponding cyclohexylamine salt: 151°C to 153°C.

Example 43

To a solution of 3.4 g. of 2-hydroxy-4-methyl-hydratropic acid sulphate dipotassium salt in 50 ml. f water Raney nickel is added as a catalyst, and the mixture is hydrogenated until a calculated amount f hydr gen is used up. Th catalyst is filtered ff and the filtrate is acidified with a 20% aque us hydrochloric acid solution. The separated oil is extracted with chloroform. Evaporation of the chlorofrm extract affords 1.5 g. (91.5%) of 4-methyl-hydratr pic acid.

Example 44

3.8 g. of N,N'-dicyclohexyl-4-methyl-(1-carboxy-1-ethyl)-phenyl-isocarbamide are dissolv d in isopropanol and to the solution obtained 0.2 g. of a 5% palladium-on-charcoal catalyst are added. The mixture is then hydrogenated at 25°C, under atmospheric pressure until a calculated amount of hydrogen is used up. Catalyst is filtered off and the filtrate is evaporated. The residue is treated with a 5% sodium carbonate solution and is filtered. The filtrate is acidified with a 20% aqueous hydrochloric acid solution and the separated oil is extracted with chloroform. The chloroform extract is dried over sodium sulphate, dried and evaporated. 1.4 g. (85%) of 4-methyl-hydratropic acid are obtained.

Example 45

3 g. of 2-hydroxy-4-methyl-hydratropic acid phenylurethane are dissolved in acetic acid. To the solution 0.4 g. of a 5% palladium-on-charcoal catalyst are added, and the mixture is hydrogenated at 25°C until a calculated amount of hydrogen is used up. The catalyst is filtered off and the filtrate is evaporated. The residue is admixed with a 10% aqueous hydrochloric acid solution and the separated oil is extracted with chloroform. The chloroform solution is dried over sodium sulphate and evaporated. 1.1 g. (67%) of 4-methyl-hydratropic acid are obtained.

Example 46

3.2 g. of [5-methyl-2-(1-carboxy-1ethyl)-phenyl]-(1-phenyl)-5-tetrazolyl ether are dissolved in 100 ml. of benzene and to the solution obtained 0.8 g. of a 5% palladium-on-charcoal catalyst are added. The mixture is hydrogenated at 35 to 40°C, under a pressure of 2.8 atm., until a calculated amount of hydrogen is used up. The catalyst is filtered off and washed with hot ethanol. The filtrate is evaporated and the residue is treated with a 5% aqueous sodium carbonate solution. After filtration the filtrate is acidified with a 20% aqueous hydrochloric acid solution and the separated oil is extracted with chloroform. The chloroform solution is dried over sodium sulphate and evaporated. 1.4 g. (85%) of 4-methylhydratropic acid are obtained.

Example 47

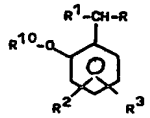
To a solution of 1.25 g. of 2-mesyloxy-5-methyl-hydratropic acid in 25 ml. of methanol 1.4 ml. of triethylamine and 0.2 g. of a 5% palladium-on-charcoal catalyst are added. The mixture is hydrogenated at 25°C, under atmospheric pressure until a calculated amount of hydrogen is used up. The catalyst is filtered off and the solution is evaporated. The evaporation residue is taken up in water, acidified with a 20% aqueous hydrochloric acid solution and shaken with ether. Ether is distilled off to give 3-methyl-hydratropic acid as an oily residue. The corresponding cyclohexylamine salt melts at 168°C to 169°C.

Example 48

1.22 g. of 2-mesyloxy-5-methyl-phenylacetic acid are dissolved in 20 ml. of methanol and to the solution obtained 1.4 ml. of triethyl amine and 0.2 g. of a 5% palladium-on-charcoal catalyst are added. Furtheron following the procedure described in Example 47 a white-crystalline product is obtained, melting at 64°C to 65°C. The product obtained is 5-methyl-phenylacetic acid.

Claims:

1. Compound of the general formula VIII and their salts,



(VIII)

wherein

R is vinyl or carboxyl,

R^1 is hydrogen, methyl, or ethyl,

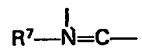
R^2 is hydrogen, fluorine or an alkyl having from 1 to 4 carbon atoms, and

R^3 is hydrogen, phenyl, alkoxy having from 1 to 6 carbon atoms, phenoxy or an optionally substituted benzoyl or thenayl, or

R^2 and R^3 together with the phenyl group they are attached to form a naphthyl group, optionally substituted with alkyl and/or alkoxy groups having from 1 to 4 carbon atoms, and

R^{10} is phenylaminocarbonyl, 1-phenyl-5-tetrazolyl, 2-benzoxazo or a group —SO_2OMe, wherein Me is a metal atom, or a group —SO_2R^6, in which

R^6 is alkyl having from 1 to 4 carbon atoms, 4-methylphenyl, amino, acylamino, alkoxycarbonylamino having from 1 to 4 carbon atoms in the alkyl moiety or a group

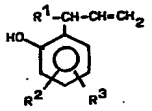


NHIR^7, in which

R is alkyl having from 1 t 4 carbon at ms, cycloalkyl having 5 to 6 carbon atoms r t lyl.

2. Compounds as claimed in claim 1 wherein R^6 is an acylamino group selected from optionally substituted benz yl and alkanoylamino having 1 to 5 carb n atoms.

3. 2-(1-Methylallyl)-phenol mesyl ester.
4. 2-Allylphen l mesyl ester.
5. 2-Allyl-1-naphthol mesyl ester.
6. 2-Allylphenol tosyl ester.
7. 2-Allyphenol-phenyl-urethane.
8. 2-Allyl-1-naphthol-phenyl-urethane.
9. 2-(1-Methylally)-phenol-phenyl-urethane.
10. 2-(1-Methylallyl)-1-naphthol-phenyl-urethane.
11. 2-Methyl-6-allylphenol mesyl ester.
12. 3-(1-Methylallyl)-4-mesyloxy-benzophenone.
13. 2-Allyl-4-methylphenol mesyl ester.
14. 2-(1-Methylallyl)-4-methylphenol mesyl ester.
15. 2-Methyl-6-(1-methylallyl)-phenol mesyl ester.
16. 2-(1-Methylallyl)-4-phenoxyphenyl mesyl ester.
17. 2-Allyl-4-phenoxyphenol mesyl ester.
18. 3-Allyl-4-mesyloxybenzophenone.
19. 2-Mesyloxyphenylacetic acid and salts thereof.
20 2-Mesyloxy-hydratropic acid and salts thereof.
21. 1-Mesyloxy-2-naphthylacetic acid and salts thereof.
22. 2-Tosyloxyphenylacetic acid and salts thereof.
23. 2-Mesyloxy-5-methylphenyl acetic acid and salts thereof.
24. 2-Mesyloxy-5-methyl-hydratopic acid and salts thereof.
25. 2-Mesyloxy-5-benzoyl-hydratropic acid and salts thereof.
26. 2-Mesyloxy-3-methyl-hydratropic acid and salts thereof.
27. 2-Mesyloxy-5-benzoyl-phenylacetic acid and salts thereof.
28. 2-Mesyloxy-3-methyl-phenylacetic acid and salts thereof.
29. 2-Mesyloxy-5-phenoxy-hydratropic acid and salts thereof.
30. 2-Mesyloxy-5-phenoxy-phenylacetic acid and salts thereof.
31. Compounds of claim 1 wherein R^{10} is mesyl.
32. Compounds of claim 1, substantially as described herein.
33. A process for preparing compounds of the general formula VIII, wherein R, R^1, R^2, R^3, and R^{10} are as defined in claim 1, which comprises reacting hydroxyaryl derivatives of the general formula V



V

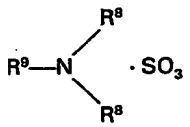
wherein R^1, R^2 and R^3 are as defined in claim 1
a) with compounds of the general formula VI

$$R^5—Y \qquad (VI)$$

wherein
R^5 is 1-phenyl-5-tetrazolyl, 2-benzoxazolyl or a group $—SO_2R^6$, in which
R^6 has the same meaning as defined in claim 1, and
Y represents a halogen atom, or
b) with phenylisocyanate, or
c) with compounds of the general formula IX

$$R^7—N=C=N—R^7 \qquad (IX)$$

wherein R^7 has the same meaning as defined in claim 1, or
d) with compounds of the general formula X

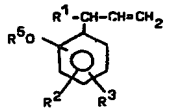


(X)

wherein
R^8 is alkyl having from 1 t 4 carb n atoms, and
R^9 is alkyl having from 1 to 4 carbon atoms or phenyl, or
e) with pyridine-sulphur trioxide c mplex, and if desired oxidizing a compound of the general

formula VIII obtained, in which R is a vinyl group into another compound of the general formula VIII, in which R represents a carboxyl group.

34. A process as claimed in claim 33 for the preparation of comp unds of the general formula XIII,



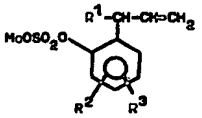
(XIII)

wherein R^1, R^2 and R^3 are as defined in claim 1, R^5 is as defined in claim 33, which comprises reacting in the process variant a) hydroxyaryl derivatives of the general formula, V, wherein R^1, R^2, and R^3 are as defined in claim 1, with methane sulphonylchloride, *p*-toluene sulphonylchloride, sulphamoyl chloride, N-benzoyl-sulphamoyl chloride or N-methoxy-sulphamoyl chloride, in water and/or in an organic solvent.

35. A process as claimed in claim 34, in which as a solvent pyridine, acetone, methylene chloride or benzene is used.

36. A process as claimed in claim 34, which comprises carrying out the reaction in the presence of an inorganic or organic base.

37. A process as claimed in claim 33 for the preparation of compounds of the general formula XVI



(XVI)

wherein

R^1, R^2, R^3 and Me have the meanings defined in claim 1, which comprises reacting in process variant d) hydroxyaryl derivatives of the general formula V, wherein R^1, R^2 and R^3 are as defined above, with sulphur trioxide complexes of N,N-dimethylaniline, N-N-diethylaniline or trimethylamine in an organic solvent, and treating the reaction mixture obtained with an aqueous solution of an inorganic base.

38. A process as claimed in claim 37, wherein an excess amount of said base is employed.

39. A process as claimed in claim 33 for the preparation of compounds of the general formula XVI, wherein R^1, R^2, R^3 and Me have the meanings defined in claim 1, which comprises reacting in process variant e) hydroxyaryl derivatives of the general formula V, wherein R^1, R^2 and R^3 are as defined above, with the sulphur trioxide complex of pyridine and subsequently treating the reaction mixture obtained with an aqueous solution of an inorganic base.

40. A process as claimed in claim 39, wherein an excess amount of said base is employed.

41. A process as claimed in claim 33 for the preparation of compounds of the general formula VIII, in which R represents a carboxyl group, which comprises oxidizing a corresponding compound of the general formula VIII in which R is vinyl, in the presence of an organic solvent, with potassium permanganate.

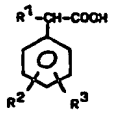
42. A process as claimed in claim 41, in which in addition to potassium permanganate an alkali metal periodate, is used as an oxidizing agent.

43. A process as claimed in claim 41 or 42, which comprises carrying out the oxidation in the presence of acetic acid and of a phase-transforming catalyst.

44. A process as claimed in claim 33, substantially as hereinbefore described.

45. A process as claimed in claim 33, substantially as hereinbefore described with reference to Examples 1—33.

46. A process for the preparation of an arylacetic acid of the general formula



(I)

wherein R^1, R^2 and R^3 are as defined in claim 1, which comprises catalytically hydrogenating a compound of general formula (VIII) as defined in claims 1, 2 or 31 wherein R is carboxyl.

47. A process according to claim 46 wherein there is used as starting material a compound of any of claims 19—30.

48. A pr cess according t claim 46, substantially as defined herein.

49. A process according to claim 46, substantially as defined herein with reference t Examples 34—48.

50. Compounds of the general formula (VIII) as defined in claim 1 with the modification that R^6 is lower alkoxyamino, especially methoxyamin .

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